

Summary of Technical Comments on Draft Ethylene Oxide IRIS Assessment

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Summary

Since 2006, ACC has submitted constructive recommendations to improve the scientific basis, objectivity, and predictability of the Ethylene Oxide IRIS Assessment.

To date, EPA has not incorporated these suggestions and has not adequately responded to these technical comments.

Summary

EPA's unit risk for E0 has essentially remained unchanged in draft assessments from 2006 through 2014: unit risk = ~ 0.0018 per $\mu\text{g}/\text{m}^3$ (10^{-6} risk-specific concentration ~ 0.4 ppt)

Based on the comments submitted on

- risk determination assumptions
- calculations
- modeling
- MOA
- uncertainties
- lack of transparency

alternatives should be considered.

Charge Questions #4 & #7

Jane Teta has commented that EPA has not adequately addressed

- **NIOSH exposure assessment uncertainties**
- **Value of UCC data for increasing the power of the study**
- **Potential selection bias for the breast cancer study**
- **Inconsistencies in the breast cancer study exposure-response trends**

Recommended inclusion of UCC data and consideration of dropping breast cancer as target organ

Charge Question #3 & #7

Richard Irons has demonstrated that

The consensus in evidence-based medicine does NOT support grouping all lymphohematopoietic cancers or all lymphoid cancers in a single category because these classifications contain many diverse cancers that are NOT related with respect to cells of origin, mechanisms, or etiology.

Recommended analyzing by distinct disease entities

Charge Questions #5 & #7

Dick Albertini commented that EPA should reconsider presenting only a linear, non-threshold extrapolation for all tumors in recognition of

- **Uncertainty in the MOA**
- **Evidence of weak mutagenicity and non-linearity in the dose response for adduct formation and mutation at low exposures**
- **Several examples where thresholds were demonstrated**

Charge Questions #2, #3, & #7

Bob Sielken presented 6 points to consider and concluded

The best exposure-response model for all endpoints (including breast cancer) is a continuous log-linear Cox proportional hazards model based on cumulative exposure (not log cumulative exposure) and that is fitted to the individual data.

Charge Questions #5 & #7

Chris Kirman concluded

- Potency estimate is not consistent with the relative toxic and mutagenic (weak) potencies
- 1×10^{-6} risk-specific concentrations calculated for EO using EPA's unit risk value are orders of magnitude lower than
 - Ambient EO concentrations
 - EO in exhaled breath
 - Endogenous EO concentrations

Summary

One of several plausibility checks

Ethylene Oxide is a weak rodent carcinogen and weak mutagen. Without sufficient epidemiology evidence, the Negligible Risk value (1 in 1,000,000) is not expected to be an exposure level that would result in an internal dose of EO that is less than the endogenous level and that would result in the ranking of Ethylene Oxide as a potent carcinogen.

Selected Chemicals Comparison of Negligible Risk (1 in 1,000,000)*

*This Table is calculated using unit risk values available at <http://www.epa.gov/iris/>.

Chemical	<i>De minimis</i> Concentration (µg/m3)	EO is more potent in developing cancer by
Benzene	0.45	640x
Propylene oxide	0.30	430x
2,4,6-Trichlorophenol	0.30	430x
Vinyl chloride	0.23	330x
Formaldehyde	0.08	110x
1,1,2,-Trichloroethane	0.06	86x
1,3-Butadiene	0.03	43x
PCBs	0.01	14x
1,2-Diphenylhydrazine	0.005	7x
Toxaphene	0.003	4x
N-Nitrosopyrrolidine	0.002	3x
Heptachlor	0.0008	1
Ethylene Oxide (draft)	0.0007	1

Conclusion

When plausibility checks are made and none of the outcomes is determined to be reasonable, it suggests that there is something incorrect with the

- risk determination assumptions**
- calculations**
- modeling**
- and/or MOA**

and that alternatives need to be examined.

Question on the EO *De minimis* value

HOW SMALL IS 0.0007 $\mu\text{g}/\text{m}^3$ of EO?

**Equals 400 parts per quadrillion or
0.4 parts per trillion (ppt)**

- **0.4 ppt is like a ~2.5 inch leap on the 93,000,000 mile journey to the sun**
- **0.4 ppt is like one second out of 80,000 years**

